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Synthesis and Glycosidase Inhibitory Activities of 2-(aminoalkyl)pyrrolidine-3,4-diol Derivatives

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Abstract—Several 2-(aminomethyl)-and 2-(2-aminoethyl)-pyrrolidine-3,4-diol derivatives have been assayed for their inhibitory activities towards glycosidases. Good inhibitors of α-mannosidases must have the (2*R*,3*R*,4*S*) configuration and possess 2-(benzylamino)methyl substituents. Stereomers with the (2*S*,3*R*,4*S*) configuration are also competitive inhibitors of α-mannosidases, but less potent as they share the configuration of C(1), C(2), C(3) of β-D-mannosides rather than that of α-D-mannosides. Interestingly, (2*S*,3*R*,4*S*)-2-{2-[(4-phenyl)phenylamino]ethyl}pyrrolidine-3,4-diol (**12g**) inhibits several enzymes, for instance α-L-fucosidase from bovine epididymis ($K_i = 6.5\,\mu M$, competitive), α-galactosidase from bovine liver ($K_i = 5\,\mu M$, mixed) and α-mannosidase from jack bean ($K_i = 102\,\mu M$, mixed). Diamines such as (2*R*,3*S*,*4R*)-2-[2-(phenylamino) or 2-(benzylamino)ethyl]pyrrolidine-3,4-diol (***ent*-12a**, ***ent*-12b**) inhibit β-glucosidase from almonds ($K_i = 13$–$40\,\mu M$, competitive).

Introduction

Monosaccharide mimetics such as 1,4-dideoxy-1,4-iminoalditols (hydroxylated pyrrolidines) are well-known as glycosidase inhibitors.[1,2] Their enzymatic inhibition arises from their ability, after protonation in physiological media, to mimick the structure of the oxycarbeniun ion liberated during the enzyme catalyzed hydrolytical process. It is observed however, that in many instances hydroxylated pyrrolidines are not selective, presenting a wide range of enzymatic inhibition. This lack of selectivity is probably due to their higher conformational flexibility compared to their piperidine analogues.

The selectivity in enzyme inhibition can be improved by providing the iminosugar with some information of the aglycon that is liberated in the enzymatic hydrolysis in addition to the information about the structure of the glycosyl moiety that is cleaved away and that mimicks the oxycarbenium ion intermediate. Therefore, the introduction of additional groups in the iminosugar could lead to new more potent and more selective enzyme inhibitors.[3] It is also important[4] to point out that the stability of a given compound towards acid hydrolysis and its permeability through membranes are important requirements for a compound to become a useful drug. Hence, hydrolytically stable C–C links and lipophilic moieties that common sugars lack are important structural features for potentially efficient and selective glycosidase inhibitors. Approaches have been made to fulfill those requirements such as imino-*C*-disaccharides[5] and imino-*C*-glycosides of heterocycles.[6] Additionally, the introduction in the aglycon moiety of a second amino group able to increase the number of electrostatic interactions with the carboxylic groups of the active site of the glycosidase, together with the presence of substituents capable of establishing stabilizing hydrophobic interactions with other sites of the enzyme, is an approach that might be useful. *Meso*-2,3-dihydroxypyrrolidine **1** is a weak and non-selective enzyme inhibitor presenting a wide range of enzymatic inhibition.[7] The introduction of a methyl group in C-2 as in compound **2** does not improve the enzymatic properties.[8] We have already proposed[7] (Fig. 1) a dicationic mimetic of the transition state (or the intermediate) corresponding to the hydrolytical process, to account for an increase of the electrostatic interactions with the

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carboxylate groups of the enzyme in α-mannosidase inhibitors. We have demonstrated that the introduction of an aryl(alkyl)aminomethyl side chain at C-2 of dihydroxypyrrolidine **1** causes a remarkable enhancement on activity and selectivity. Thus, diamines of type **3** can be highly selective and competitive inhibitors of α-mannosidases and we have reported[9] a quick combinatorial approach for their preparation. The best results in this series towards α-mannosidases are obtained with derivatives containing 4-phenylbenzylamino ($K_i = 2.5\,\mu M$) and (*R*)-indenylamino ($K_i = 2.3\,\mu M$) moieties (competitive inhibitors).[7b]

Several polyhydroxylated amino and aminoalkyl pyrrolidines have also been described. The synthesis of 5-amino-1,4-dideoxy-1,4-imino-D-mannitol hydrochloride **4**, has been reported by Jäger and co-workers;[10] in contrast to its analogue 1,4-dideoxy-1,4-imino-D-mannitol, which is a potent inhibitor of α-mannosidases, **4** does not inhibit this enzyme. Reynolds and co-workers[11] have prepared 1- and 6-aminoalkyl derivatives of 2,5-dideoxy-2,5-imino-D-glucitol (**5** and **6**) that present antibacterial activity potentially useful in the treatment of tuberculosis (Fig. 2).

Stütz and co-workers have described the synthesis and enzymatic inhibitory activity of derivatives of 1-amino-1,2,5-trideoxy-2,5-imino-D-mannitol. Alkylamino derivatives[12] of type **7** (*R* = 6-hydroxyhexyl, 3-aminopropyl) are good inhibitors of α-glucosidases ($K_i = 10$–$25\,\mu M$), while amides of type **8**[13] (*R* = undecyl, phenylethyl, naphthyl, coumarinyl) present inhibitory activities towards β-glucosidases in the nanomolar range ($K_i = 1.2$–$550\,nM$). On their side, Wong and coworkers[14] have reported the synthesis of **8** (*R* = Me) which is a potent inhibitor of β-*N*-acetylglucosaminidases ($K_i = 0.2\,\mu M$). Additionally, the same authors[15] reported the synthesis and enzymatic activity of derivatives of 1-alkyl(aryl) amino-1,2,5-trideoxy-2,5-imino-D-galactitol **9** obtained by reductive amination and Strecker condensation.

Thus, compound **9a** ($R = C_{10}H_{21}$, $R' = H$) and **9b** ($R = C_2H_4Ph$, $R' = H$) showed good inhibition towards α-mannosidases ($K_i = 10\,\mu M$) and α-*N*-acetylgalactosaminidases ($K_i = 29.4\,nM$), respectively, while the same derivatives with $R' = CH_2NH_2$ or $CONH_2$ were found to be less active towards the same enzymes.

Recently it has been claimed that the presence of a hydroxy group at C-2 of the pyrrolidine ring enhances strongly its enzymatic activity and selectivity. Thus, hemiaminals **10**[8] are potent inhibitors in the sub-μM range of α-mannosidases (jack bean), β-glucosidases (almonds) and β-galactosidases (coffee beans and *E. Coli*) while their corresponding enantiomers ***ent*-10**[8,16] are inhibitors of α-mannosidases and α-fucosidases with K_i between 3 and 20 μM. Other hemiaminals **11** and ***ent*-11**[17] have been reported, both enantiomers present similar inhibitory activities. They are moderate inhibitors of β-glucosidases (almonds) and good competitive inhibitors of α-mannosidases (jack bean and almonds) with $K_i = 0.94$–$2.5\,\mu M$ (Fig. 3). Unfortunately, because of their hemiaminal structure, **10** and **11** present the inconvenience of their poor stability.

Looking for new, easily accessible, chemically stable and selective enzymatic inhibitors, we report here a

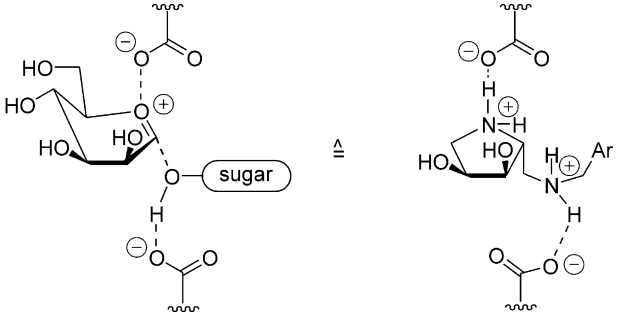


Figure 1.

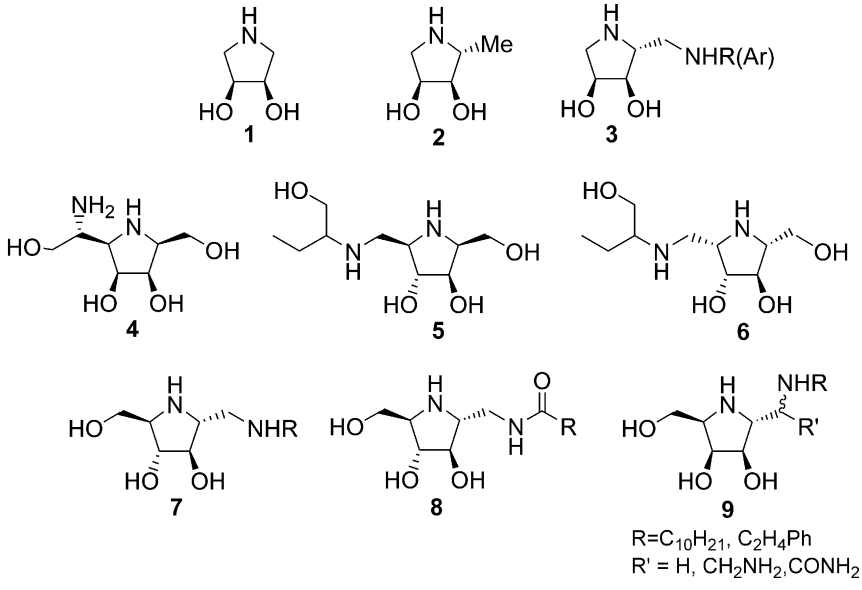


Figure 2.

study that evaluates the importance for the inhibitory activity towards glycosidases of the configuration of centers C(2), C(3) and C(4) on the pyrrolidine moiety of these compounds. We examine also the influence of the aryl(alkyl) substituent, and of the nature of the spacer between the nitrogen center of the pyrrolidine ring and that of the aminoalkyl side chain. With this goal in mind, we have prepared derivatives of (2*S*,3*R*,4*S*), (2*R*,3*R*,4*S*), (2*R*,3*S*,4*R*) and (2*S*,3*S*,4*R*)-2-alkyl(aryl) aminoethyl-3,4-dihydroxypyrrolidines (**12**, ***ent*-12**, **13** and ***ent*-13**) and of (2*S*,3*R*,4*S*)-2-(*N*-alkyl(aryl) aminomethyl-3,4-dihydroxypyrrolidines (**14**) and have assayed these compounds towards 25 commercially available glycosidases.

The best results are observed with systems having aromatic substituents. Enzyme specificity depends on the absolute configuration of the iminosugars. For instance, while compounds **12**, **13** and **14** are good inhibitors of α-mannosidases, ***ent*-12** and ***ent*-13** are good inhibitors of β-glucosidases (Fig. 4). In both cases they are moderate inhibitors of β-galactosidases.

α-Mannosidases inhibitors are of importance in anticancer therapies because they inhibit the biosynthesis of *N*-linked glycoproteins associated with metastasis and cancer progression. Natural compounds such as swainsonine (**15**)[18] and mannostatin A (**16**)[19] are among the most potent inhibitors of α-mannosidases and have proved their efficiency in a variety of antitumor and antiviral screenings (Fig. 5).[20]

On their side, α-glucosidase inhibitors are of key importance in the replication of the AIDS virus (HIV), particularly in the formation of its envelope glycoprotein-mediated fusion at the binding step. *N*-Butyldeoxynojirimycin (**17**), one of the most potent α-glucosidase inhibitors, has been considered as a potential anti-HIV therapeutic agent.[21] Other strong α-glucosidase inhibitors such as castanospermine (**18**), 1-deoxynojirimycin (**19**),[22] and bromoconduritol (**20**)[23] reduce HIV-1 infectivity in vitro.[24]

Results and Discussion

The syntheses of 2-alkyl(aryl)-3,4-dihydroxypyrrolidines **12**–**14,** have been carried out by reductive amination of the corresponding pyrrolidine-carbaldehydes followed by deprotection. In the case of diamine **12j**, reaction took place between diamine **36**[25] and biphenyl-4-carbaldehyde. Alternatively, alkylaminopyrrolidines (**12k** and ***ent*-12g**) were obtained from the corresponding pyrrolidine-carboxylic acids after amidation reaction and subsequent reduction and deprotection. (Scheme 1).

Pyrrolidine-carbaldehydes **25** and **26** were prepared according to Buchanan's methodology.[26] Starting from

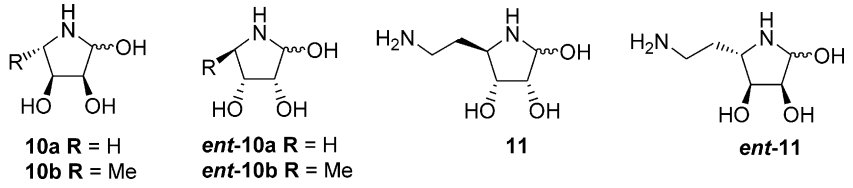
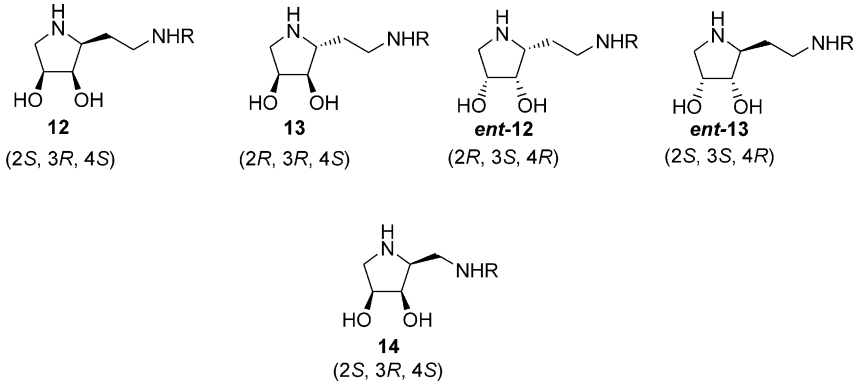


Figure 3.



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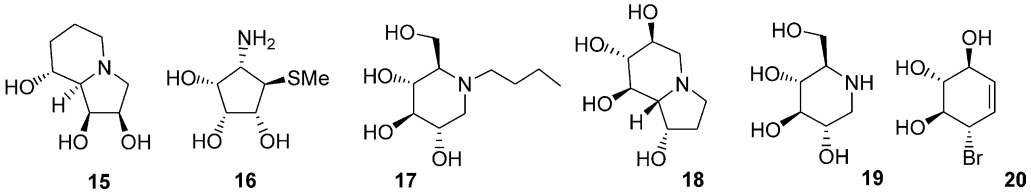

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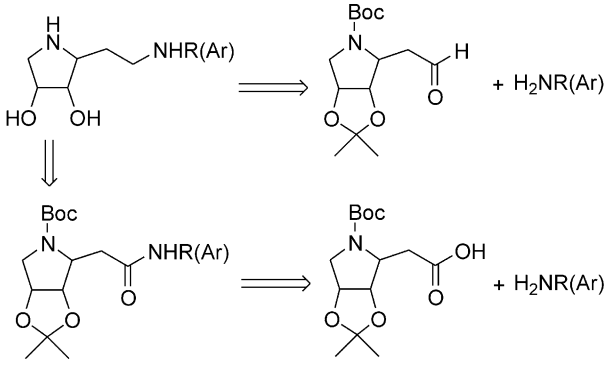


Scheme 1.

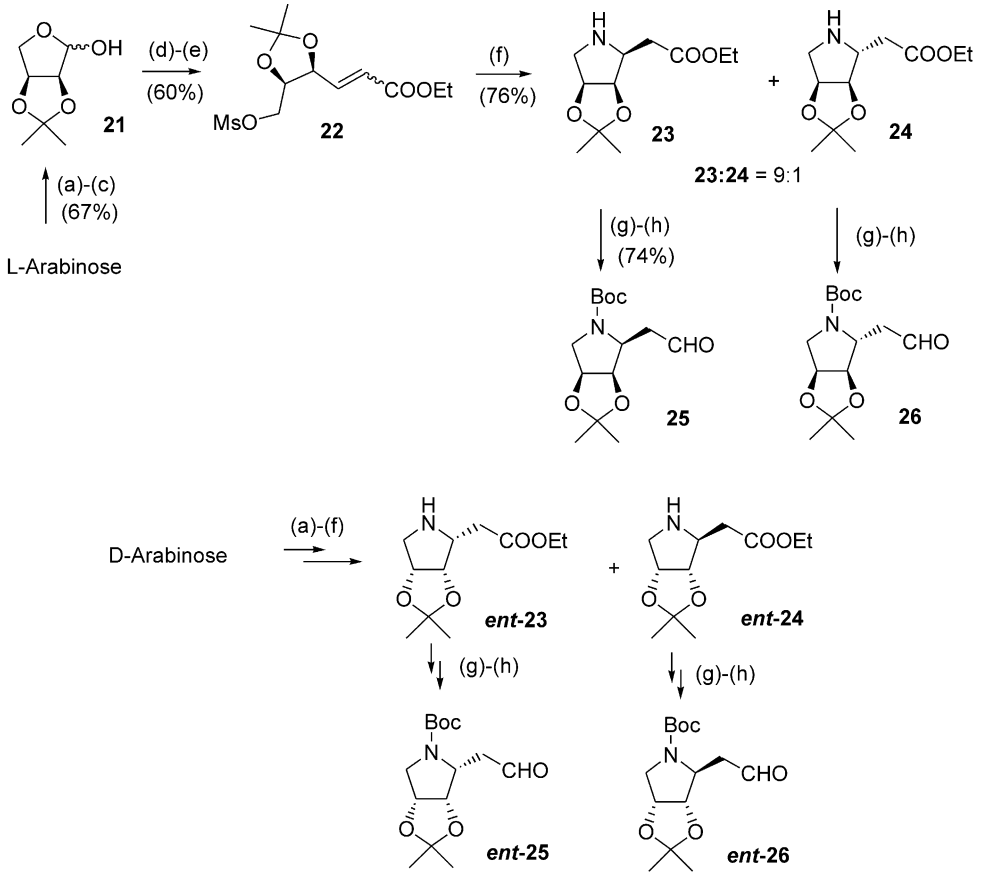
2,3-isopropylidene-L-erythrose,[26b] a mixture of pyrrolidines **23** and **24** in a ratio 9:1 was obtained after Wittig olefination, addition of ammonia and intramolecular displacement of the mesylate.

Boc protection and reduction with DIBALH gave the corresponding aldehydes **25**[5m,5n] and **26**. In a similar way enantiomerically pure aldehydes ***ent*-25**[25] and ***ent*-26** were obtained from D-arabinose (Scheme 2).

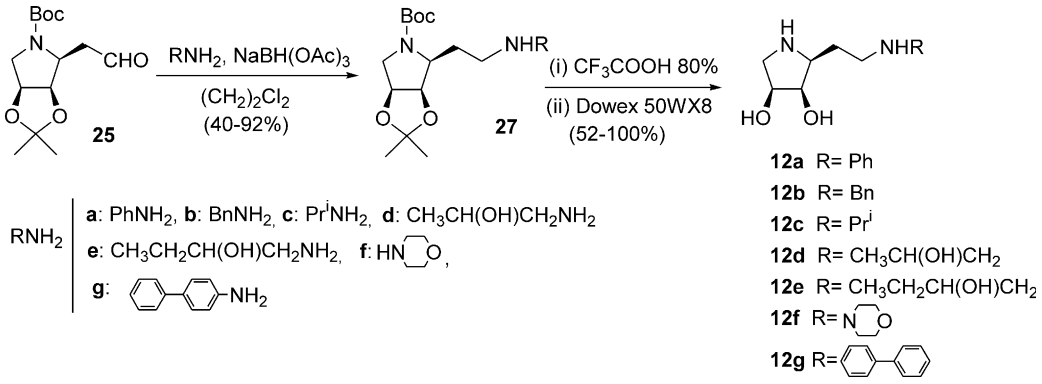
The minor aldehydes **26** and ***ent*-26** were not isolated and immediately reacted in the following step. Reaction of aldehyde **25** with a small library of amines followed by in situ reduction with $NaBH(OAc)_3$ and subsequent deprotection with aqueous CF_3COOH gave the corresponding diamines **12** in good yields (Scheme 3). In the case of minor aldehyde **26** (Scheme 4) reductive amination with aniline gave **28a** (45% from **24**) which was subsequently deprotected to give diamine **13a**.

The same procedure as described above was applied to the preparation of diamines ***ent*-12** and ***ent*-13a** from the enantiomerically pure pyrrolidine-carbaldehydes ***ent*-25** and ***ent*-26** (Schemes 5 and 6). For compound ***ent*-25**, reaction with aniline, benzylamine, 1-aminobutanol, and morpholine gave protected diamines ***ent*-27** in moderate-to-good yields that, after acidic cleavage, furnished diamines ***ent*-12** in 66–100% yield. Aldehyde ***ent*-26** was obtained from minor epimer ***ent*-24**, and made immediately react with aniline in the presence of $NaBH(OAc)_3$ furnishing protected diamine ***ent*-28a** in 55% overall yield from ***ent*-24**. Acidic hydrolysis gave ***ent*-13a** in 84% yield.

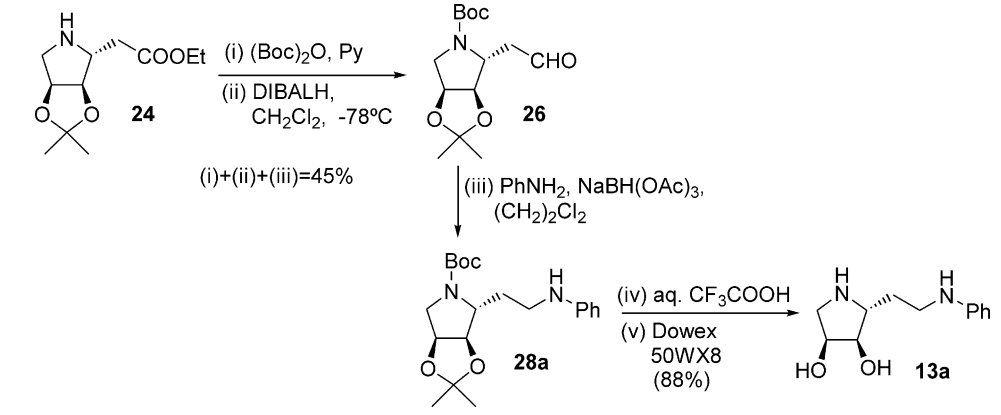
The preparation of compounds **14** was carried out by reductive amination of aldehyde **30** with benzylamine and (*R*)-1-aminoindane and subsequent treatment with aqueous CF_3COOH. Compound **30** was obtained[7b] by Swern oxidation of the intermediate primary alcohol **29**, that was obtained from D-ribose following the method described by Kim and co-workers.[27]



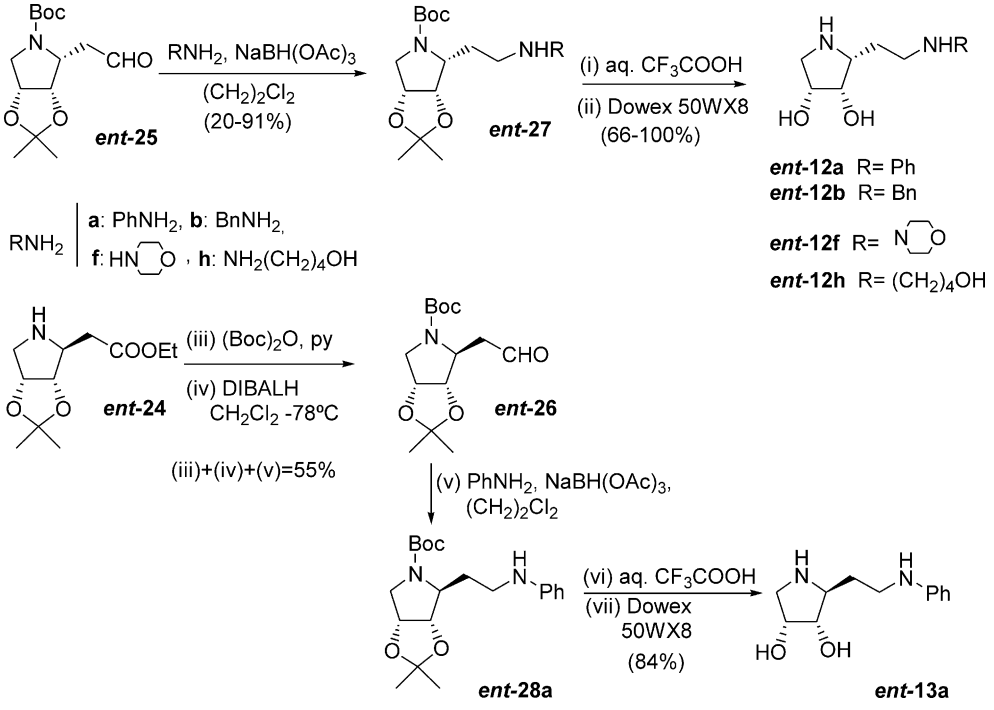
Scheme 2. Reaction conditions: (a) acetone, H_2SO_4; (b) $NaIO_4$, H_2O; (c) (i) NaOH 1 M, (ii) HCl 1 M; (d) $Ph_3P{=}CHCOOEt$, CH_2Cl_2 refl.; (e) MsCl, Py; (f) NH_3, EtOH, (g) $(Boc)_2O$, Py; (h) DIBALH, CH_2Cl_2, −78 °C.



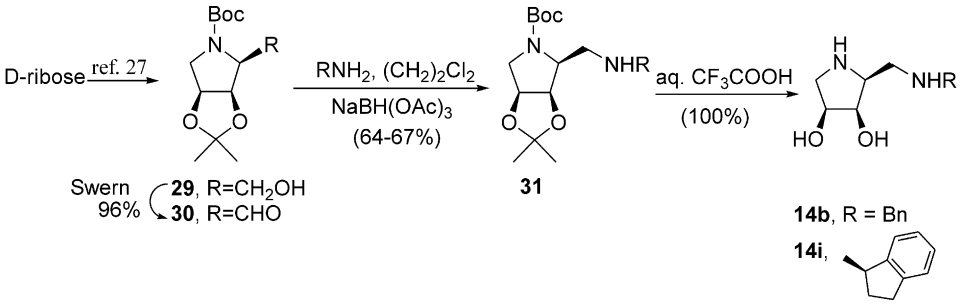
Scheme 3.



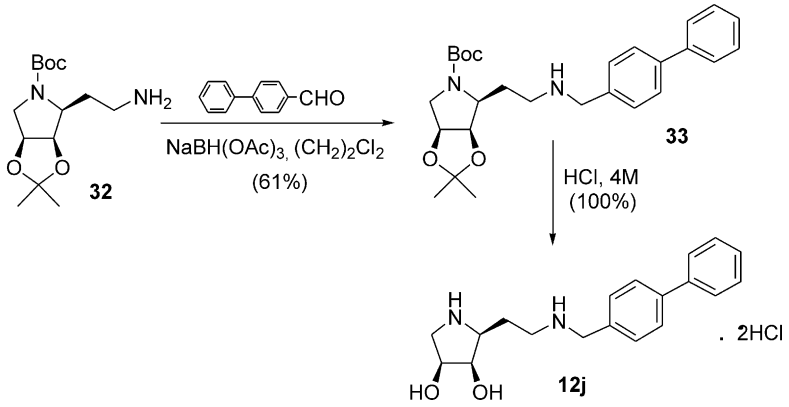
Scheme 4.



Scheme 5.



Scheme 6.



Scheme 7.

Diamine **32**[25] was made react with biphenyl-4-carbaldehyde under the same conditions furnishing diamine **33** that, after deprotection with 4 M HCl gave **12j** in quantitative yield (Scheme 7).

Finally, amidation reaction between pyrrolidine carboxylic acids **34** and ***ent*-34** and α-naphthylamine and biphenyl-4-amine, respectively, afforded compounds **35k** and ***ent*-35g** that, after reduction with $BH_3.SMe_2$ and acidic deprotection, gave diamines **12k** and ***ent*-12g** (Scheme 8).

Enzymatic inhibitory studies

Diamines **12**–**14**, have been tested for their inhibitory activity towards 25 commercially available glycosidases. The data are summarised in Tables 1 and 2.

As expected, the absolute configuration of the stereogenic centers in the pyrrolidine ring have noticeable influence on the inhibitory selectivity. Thus, (2*S*,3*R*,4*S*)-2-alkyl(aryl)aminoethyl and aminomethyl pyrrolidines **12** and **14** have shown to be moderate-to-good inhibitors of α-mannosidases, while derivatives ***ent*-12** of (2*R*,3*S*,4*R*) configuration were inactive towards these enzymes, but presented good inhibitory activities towards β-galactosidases and β-glucosidases.

Diamine **36**[25] (Fig. 6) is a moderate inhibitor of α-mannosidase from jack bean (52% of inhibition at 1 mM) and is ignored by α-mannosidase from almonds. Derivatives **12c** ($R = Pr^i$), **12d** (R = 2-hydroxypropyl), **12e** (R = 2-hydroxybutyl), and **12f** (R = -morpholine), showed similar inhibition activities as **36**. In contrast, compounds **12b** (R = Bn) and **12g** (R = biphenyl) are more potent inhibitors suggesting the intervention of stabilizing hydrophobic interactions between the aromatic ring of the inhibitor and the enzyme.

In the case of compounds **14** with (aryl)aminomethyl side chains, the activity and selectivity towards α-mannosidases is notably increased. This is an additional evidence, as it has been reported,[7a] of the importance of the size of the spacer between the nitrogen center of the pyrrolidine moiety and that of the side chain. The optimal results are observed for 1,2-diamines. It is worth noting that compound **12g** with a biphenyl moiety is a relatively potent inhibitor of α-L-fucosidases (bovine epididymis) (K_i = 6.5 μM). The efficiency in the inhibitory activity of biphenyl derivatives was precedent,[7b] having been found that molecular motifs containing a biphenyl moiety are high affinity-ligands for proteins.[28] Compound **12a** (R = Ph) presents also moderate inhibition 40% towards this enzyme. Compounds of this series were also moderate-to-good inhibitors of β-galactosidases like **12a** (R = Ph, 64%), **12c** ($R = Pr^i$, 33%), **12e** ($R = C_2H_5CH(OH)CH_2$, 95%), **12f** (R = morpholine, 29%), **12g** (R = biphenyl, 90%, K_i = 5 μM), **12j** (R = biphenylmethyl, 85%), **12k** (R = naphthyl, 95%), **14b** (R = Bn, 37%) and **14i** (R = indenyl, 33%) at 1 mM concentration (see Table 1).

The inhibition towards β-galactosidases and α-mannosidases can be explained taking into account the different conformations of the flexible pyrrolidine moiety that can mimic C-2 and C-3 of D-mannose or C-3 and C-4 of D-galactose (Fig. 7). The competitive inhibition towards α-fucosidases can be explained by the resemblance of C-

Table 1. Inhibitory activities of compounds **12a–12g, 12j, 12k, 13a, 14b, 14i and 36**. Percentage of inhibition at 1 mM concentration, IC_{50} and K_i values in μM, when measured at optimal pH, 25 °C. All inhibitors are competitive (Lineweaver–Burk plots) except when indicated (M = mixed type of inhibition). NI = no inhibition at 1 mM concentration

Enzymes:	**12a**	**12b**	**12c**	**12d**	**12e**	**12f**	**12g**	**12j**	**12k**	**13a**	**14b**	**14i**	**36**
α-L-fucosidase													
Bovine epididymis	40%	NI	NI	NI	NI	NI	78% (C) (IC_{50} = 63 μM) **K_i = 6.5 μM**	NI	NI	NI	NI	NI	NI
Human placenta	28%	NI	NI	NI	NI	NI	33%	NI	NI	NI	NI	NI	NI
β-Galactosidase													
Bovine liver	64% (IC_{50} = 630 μM)	NI	33%	NI	95%	29%	90% (M) (IC_{50} = 45 μM) **K_i = 5 μM**	85%	95%	NI	37%	33%	NI
Jack beans	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	30%	47%	NI
α-Glucosidase (isomaltase)													
Baker yeasts	NI	NI	NI	NI	NI	NI	78% (IC_{50} = 470 μM)	NI	NI	NI	60%	66%	22%
Amyloglucosidase													
Aspergillus niger	NI	27%	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	24%
Rhizopus mold	NI	23%	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
β-glucosidase													
Almonds	NI	NI	NI	NI	22%	NI	48%	NI	NI	NI	47%	31%	NI
caldocellum saccharolyticum	31%	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	25%	NI
α-mannosidase													
Jack beans	25%	57% (M) (IC_{50} = 620 μM) **K_i = 360 μM**	25%	54% (IC_{50} = 1 mM)	55% (IC_{50} = 830 μM)	41%	70% (M) (IC_{50} = 360 μM) **K_i = 102 μM**	59%	53%	33%	72% (C) (IC_{50} = 361 μM) **K_i = 8.7 μM**	73% (C) (IC_{50} = 397 μM) **K_i = 12.1 μM**	52% (IC_{50} = 1 mM)
Almonds	NI	21%	22%	20%	24%	39%	32%	NI	NI	NI	44%	38%	NI

NI towards the following enzymes: **α-galactosidases** from coffee beans, *Aspergillus niger* and *Escherchia coli;* **β-galactosidase** from-*Escherichia coli*, *Aspergillus niger* and *Aspergillus orizae*; **α-glucosidases** (maltase) from yeast and rice; **β-mannosidase** from *Helix pomatia;* **β-xylosidase** from *Aspergillus niger;* **α-*N*-Acetylgalactosaminidase** from chicken liver; **β-*N*-Acetylglucosaminidases** from jack bean, bovine epididymis A and bovine epididymis B.

Table 2. Inhibitory activities of compounds ***ent*12a**, ***ent*-12b**, ***ent*-12f**, ***ent*-12g**, ***ent*-12h**, ***ent*-13a** and **37**. Percentage of inhibition at 1 mM concentration, IC_{50} and K_i values in μM, when measured at optimal pH, 25 °C. All inhibitors are competitive (Lineweaver–Burk plots) except when indicated (M = mixed type of inhibition). NI = no inhibition at 1 mM concentration

Enzymes:	***ent*-12a**	***ent*-12b**	***ent*-12f**	***ent*-12g**	***ent*-12 h**	***ent*-13a**	**37**
α-Galactosidase							
Escherchia coli	NI	NI	NI	NI	NI	47%	NI
Coffee beans	NI	NI	NI	73%	NI	NI	
β-Galactosidase							
Escherichia coli	42%	NI	NI	93% (M) (IC_{50} = 73 μM) **K_i = 1.5 μM**	NI	NI	NI
Bovine liver	86% (M) (IC_{50} = 180 μM) **K_i = 20 μM**	46%	32%	97%	45%	NI	NI
Aspergillus niger	59% (IC_{50} = 640 μM)	69% (IC_{50} = 310 μM)	28%	NI	44%	NI	NI
Aspergillus orizae	NI	27%	NI	NI	NI	NI	NI
Amyloglucosidase							
Rhizopus mold	NI	24%	NI	NI	NI	NI	NI
β-glucosidase							
Almonds	94% (C) (IC_{50} = 180 μM) **K_i = 13 μM**	87% (C) (IC_{50} = 110 μM) **K_i = 40 μM**	40%	93% (C) (IC_{50} = 49 μM) **K_i = 20 μM**	35%	95% (C) (IC_{50} = 30 μM) **K_i = 14 μM**	NI
Caldocellum saccharolyticum	36%	NI	NI	NI	NI	NI	NI
α-mannosidase							
Jack beans	NI	NI	23%	NI	NI	58% (IC_{50} = 613 μM)	NI
17-Almonds	NI	NI	NI	NI	NI	49% (IC_{50} = 1 mM	NI
α-*N*-Acetylgalacto saminidase							
Chicken liver	68% (IC_{50} = 360 μM)	NI	NI	NI	NI	NI	NI
β-*N*-Acetylglucosa minidase							
Jack bean	NI	51%	NI	NI	NI	NI	NI

NI towards the following enzymes: α-L-**fucosidase**s from bovine epididymis and human placenta; **α-galactosidases** from coffee beans and *Aspergillus niger;* **α-galactosidase** from coffee beans and *Aspergillus niger;***β-galactosidase** from *jack bean*; **α-glucosidases** (maltase) from yeast and rice; **α-glucosidases** (isomaltase) from Baker yeast; **amyloglucosidase** from *Aspergillus niger*; **β-mannosidase** from *Helix pomatia;* **β-xylosidase** from *Aspergillus niger;* **β-*N*-Acetylglucosaminidases** from jack bean, bovine epididymis A and bovine epididymis B

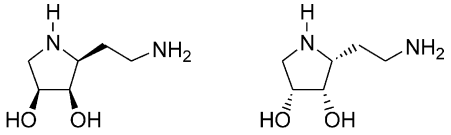


Figure 6.

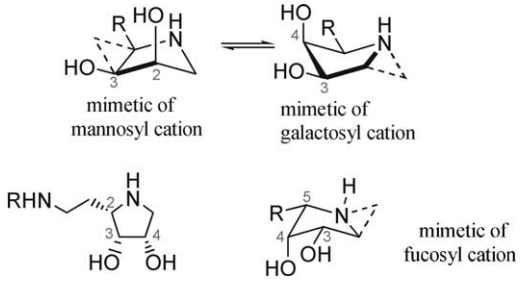
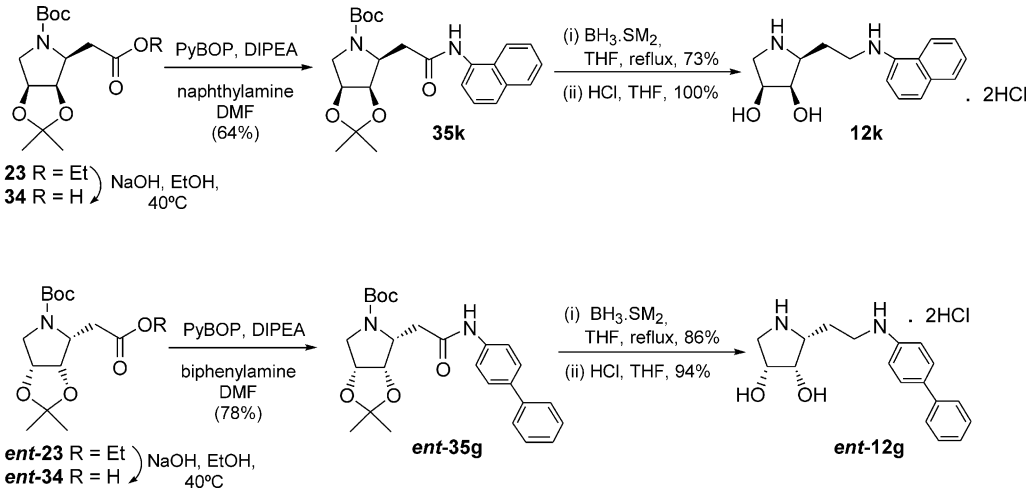


Figure 7.

2,3,4 after rotation of the molecule, with C-3,4,5 of the fucopyranosyl moiety. Compound **13a**, C-2 epimer of **12a**, is totally inactive except for a weak inhibition (33% at 1 mM concentration) towards α-mannosidases.

Diamine **37** was inactive towards the 25 enzymes analyzed, however derivatives ***ent*-12a**, ***ent*-12b**, ***ent*-12f**, ***ent*-12h** and ***ent*-12g** presented activity towards β-galactosidases from bovine liver, *Aspergillus niger* and *Escheriiccia coli*. Compounds ***ent*-12a** and ***ent*-12g** presented the best inhibitory activities values [K_i = 20 μM (bovine liver) and K_i = 1.5 μM (*E. coli*)], respectively. These compounds are also good inhibitors of β-glucosidases from almonds, especially derivatives with aromatic substituents, confirming the importance of the aromatic ring in the lateral chain: ***ent*-12a** (*R* = Ph, 94%, K_i = 13 μM), ***ent*-12b** (*R* = Bn, 87%, K_i = 40 μM), ***ent*-12g** (*R* = biphenyl, 93%, K_i = 20 μM) and ***ent*-13a** (*R* = Ph, 95%, K_i = 14 μM), (see Table 2). However, these compounds were inactive towards α-mannosidases.

The inhibition towards β-galactosidases and β-glucosidases can be explained by the resemblance of C-2,3,4 after rotation of the molecule, with C-3,4,5 of the galactopyranosyl moiety (Fig. 8) The inhibition towards β-glucosidases can be explained considering that the pyrrolidine moiety can adopt an envelope conformation with C-4 in the apical position, then the two hydroxy groups of the pyrrolidine moiety resemble HO-2 and HO-3 of the glucopyranosyl cation.



Scheme 8.

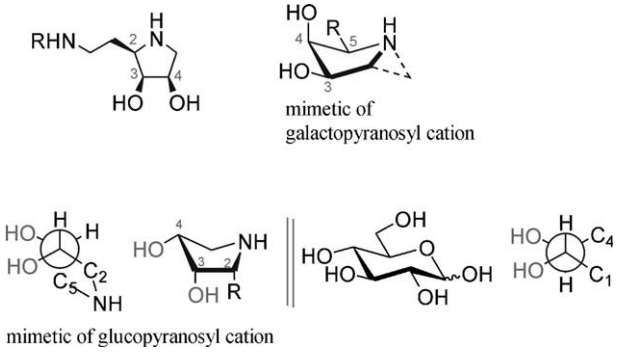


Figure 8.

Compound ***ent*-12a** and its C-2 epimer, compound ***ent*-13a**, present similar inhibitory values towards β-glucosidases from almonds. Interestingly, compound ***ent*-12a** is a good inhibitor of β-galactosidases from bovine liver ($K_i = 20\,\mu M$), while compound ***ent*-13a** ignores completely this enzyme. This fact can be explained by the configuration of C-2 that does not resemble that of C-5 of D-galactose.

Conclusion

New 2-(aminomethyl)- and 2-(2-aminoethyl)pyrrolidine-3,4-diol derivatives have been prepared and assayed for their inhibitory activities towards glycosidases. Although (2*S*,3*R*,4*S*)-2-[(benzylamino)-methyl]pyrrolidine-3,4-diol (**14b**) and (2*S*,3*R*,4*S*)-2-(inden-1-ylaminomethyl)-pyrrolidine-3,4-diol (**14i**) share the configuration of centers C(1), C(2) and C(3) of β-D-mannosides and not that of α-D-mannosides, they are moderate competitive inhibitors of α-D-mannosidase from jack bean ($K_i = 8.7\,\mu M$, $12\,\mu M$ respectively). As expected, they are not as good inhibitors as their (2*R*,3*R*,4*S*)-stereomers ($K_i = 2$–$7\,\mu M$).[7b] Apart from (2*S*,3*R*,4*S*)-2-{2-[(4-phenyl)phenylamino]ethyl}pyrrolidine-3,4-diol (**12g**) which also inhibits α-mannosidase from jack bean ($K_i = 102\,\mu M$, mixed type of inhibition), all other derivatives of these type of diamine are ignored by this enzyme. The biphenylamino compound **12g** also inhibits α-L-fucosidase from bovine epididymis ($K_i = 5\,\mu M$, mixed). The enantiomer of **12g**, ***ent*-12g** inhibits β-galactosidase from bovine liver ($K_i = 1.5\,\mu M$, mixed) and β-glucosidase from almonds ($K_i = 20\,\mu M$, competitive). The latter enzyme is also inhibited by analogues (2*R*,3*S*,4*R*)-2-[2-(phenylamino)-ethyl]pyrrolidine-3,4-diol (***ent*-12a**),-2-[2-benzylamino)-ethyl]pyrrolidine - 3,4 - diol (***ent* - 12b**) and (2*S*,3*S*,4*R*) - 2 - [2 - (phenylamino)ethyl]pyrrolidine-3,4-diol (***ent*-13a**) with inhibition constants $K_i = 13$, 40 and $14\,\mu M$ (all competitive). It should be noted that β-glucosidase from *Caldocellum saccharolyticum* ignores these diamines.

Experimental

General procedures

Optical rotations were measured in a 1.0 cm tube on Perkin–Elmer 241 MC and with a JASCO DIP-370 digital polarimeter. ^1H NMR and ^{13}C NMR spectra were obtained for solutions in $CDCl_3$, DMSO-d_6, CD_3OD and D_2O, *J* values are given in Hz and δ in ppm. All the assignments were confirmed by two-dimensional NMR experiments. The IR spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrometer. The FAB mass spectra were obtained with glycerol or 3-nitrobenzyl alcohol as matrix. TLC was performed on silica gel $60F_{254}$ (Merck), with detection by UV light and charring with Pancaldi reagent [$(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O]. Silica gel 60 (Merck, 230 mesh) was used for preparative chromatography. Solvents were dried by standard methods and were freshly distilled under N_2 prior to use.

Glycosidase inhibition assays

Well established protocol was applied.[29] We verified that the delay of inhibitor/enzyme incubation did not affect the inhibition measurements. Under standard conditions, optimal inhibitory activities were measured after 5 min of incubation.

The inhibition constants (K_i) and the type of inhibition (competitive, non-competitive, mixed) were determined from Lineweaver–Burk plots.[30] For each plot, a blank and two concentrations of inhibitor were used corresponding to IC_{50} and $IC_{50}/2$.

Reductive amination, general procedure. To a solution of *N*-*tert*-butoxycarbonyl-3,4-di-*O*-isopropylidene-3,4-diol-2-formylmethylpyrrolidine **25**[5m,5n] or *ent*-**25**[7b] (0.10 mmol) in 1,2-dichloroethane (1 mL), the corresponding amine (0.11 mmol) and $NaBH(OAc)_3$ (0.14 mmol) were added. The reaction mixture was stirred at 20 °C under N_2 for 3 h. Then, aqueous saturated solution of $NaHCO_3$, was added and extracted with AcOEt, dried (Na_2SO_4) and evaporated in vacuo. Purification of the residue gave the corresponding *N*- and *O*- protected amino pyrrolidines, all as oils.

Hydrolysis Boc and isopropylidene groups, general procedure. A solution of *N*- and *O*- protected amino pyrrolidines (0.05 mmol) in 80% aqueous CF_3COOH (1.5 mL) was left at 20 °C for 2 h. The mixture was passed through a Dowex 50WX8 column (100–200 mesh) and eluted, successively with MeOH (30 mL), H_2O (30 mL) and NH_4OH 10% (50 mL) and then was concentrated by solvent evaporation in vacuo.

The following compounds were obtained in this manner.

(2*S*,3*R*,4*S*)-2-[2-(Phenylamino)ethyl]pyrrolidine-3,4-diol (12a). Reductive amination of **25**[5m,5n] with aniline gave, after column chromatography on silica gel (ether–petroleum ether 1:5), the protected derivative **27a** (82% yield). Conventional deprotection gave **12a** (83% yield). $[\alpha]_{589}^{25}$ +20 (*c* 1.1, MeOH) ; IR (film) ν_{max} 3335, 1680, 1600, 1505, 1095, 755, 695 cm^{-1}; ^1H NMR (400 MHz, MeOD, δ ppm, *J* Hz): δ 7.11–7.06 (m, 2H, Ph), 6.66–6.57 (m, 3H, Ph), 4.33 (m, 1H, H-4), 4.04 (t, 1H, $J_{3,2}=J_{3,4}=3.7$, H-3), 3.30 (m, 1H, H-2), 3.24 (t, 2H, $J_{2'a,2'b}=7.1$, H-2′a, H-2′b), 3.20 (dd, 1H, $J_{5a,4}=7.6$, $^2J_{5a,5b}=11.7$, H-5a), 2.96 (dd, 1H, $J_{5b,4}=7.0$, H-5b), 2.08 (m, 1H, H-1′a), 1.91 (m, 1H, H-1′b); ^{13}C NMR (100.5 MHz, MeOD, δ ppm): δ 150.1 (C-1 of Ph), 130.0, 118.1 and 114.1 (Ph), 73.4, 72.8 (C-4, C-3), 61.2 (C-2), 50.4 (C-5), 42.2 (C-2′), 29.1 (C-1′). CIMS *m*/*z* 223 [100%, $(M+H)^+\cdot$]. CIMSHR: *m*/*z* 223.1441 (calcd for $C_{12}H_{18}N_2O_2+H$: 223.1446).

(2*S*,3*R*,4*S*)-2-[2-(Benzylamino)ethyl]pyrrolidine-3,4-diol (12b). Reductive amination of **25** with benzylamine gave, after column chromatography on silica gel (CH_2Cl_2–MeOH 60:1→5:1), protected derivative **27b** (46% yield). Conventional deprotection gave **12b** (60% yield). $[\alpha]_{589}^{25}$ +22 (*c* 0.8, MeOH); IR: ν_{max} 3330, 1645, 1510, 1095, 800, 705 cm^{-1}; ^1H NMR (400 MHz, MeOD, δ ppm, *J* Hz): δ 7.42–7.36 (m, 5H, Ph), 4.29 (td, 1H, $J_{4,3}=4.6$, $J_{4,5a}=J_{4,5b}=6.9$, H-4), 4.00 (dd, 1H, $J_{3,2}=4.2$, H-3), 3.85 (s, 2H, CH_2Ph), 3.21 (td, 1H, $J_{2,1'a}=J_{2,1'b}=6.9$, H-2), 3.15 (dd, 1H, $^2J_{5a,5b}=11.5$, H-5a), 2.93 (dd, 1H, H-5b), 2.81 (t, 2H, H-2′a, H-2′b), 1.99 (m, 1H, H-1′a), 1.86 (m, 1H, H-1′b); ^{13}C NMR (75.4 MHz, MeOD, δ ppm): δ 140.1 (C-1 of Ph), 129.5, 129.4 and 128.7 (Ph), 73.9, 73.3 (C-4, C-3), 61.4 (C-2), 54.3 (CH_2-Ph), 51.4 (C-5), 47.3 (C-2′), 29.9 (C-1′). CIMS *m*/*z* 237 [50%, $(M+H)^+\cdot$]. CIMSHR: *m*/*z* 237.1602 (calcd for $C_{13}H_{20}N_2O_2+H$: 237.1603).

(2*S*,3*R*,4*S*)-2-[2-(Isopropylamino)ethyl]pyrrolidine-3,4-diol (12c). Reductive amination of **25** with isopropylamine gave, after column chromatography on silica gel (CH_2Cl_2–MeOH 30:1→5:1), protected derivative **27c** (40% yield). Conventional deprotection gave **12c** (83% yield). $[\alpha]_{589}^{25}$ +10 (c 0.47, MeOH); IR ν_{max} 3280, 1400, 1095 cm^{-1}; ^1H NMR (400 MHz, MeOD, δ ppm, *J* Hz): δ 4.25 (m, 1H, H-4), 3.97 (t, 1H, $J_{3,2}=J_{3,4}=4.3$, H-3), 3.06–3.02 (m, 2H, H-2, H-5a), 2.94 (hept, 1H, $J_{H,H}=6.4$, H-1″), 2.87 (dd, 1H, $J_{5b,4}=6.2$, $^2J_{5b,5a}=11.4$, H-5b), 2.78 (m, 2H, H-2′a, H-2′b), 1.91 (m, 1H, H-1′a), 1.78 (m, 1H, H-1′b), 1.16 (d, 6H, 2 CH_3); ^{13}C NMR (100.5 MHz, MeOD, δ ppm): δ 73.9, 73.4 (C-4, C-3), 61.2 (C-2), 51.6 (C-5), 49.6 (C-1″), 45.3 (C-2′), 29.9 (C-1′), 21.9 (2 CH_3). CIMS *m*/*z* 189 [100%, $(M+H)^+\cdot$]. CIMSHR: *m*/*z* 189.1600 (calcd for $C_9H_{20}N_2O_2+H$: 189.1603).

(2*S*,3*R*,4*S*)-2-2-[((*R* and *S*)-2-Hydroxypropyl)amino] ethylpyrrolidine-3,4-diol (12d). Reductive amination of **25** with *rac*-2-hydroxypropylamine gave, after column chromatography on silica gel (CH_2Cl_2–MeOH 35:1→10:1), protected derivative **27d** (40% yield). Conventional deprotection gave **12d** (98% yield). ^1H NMR (400 MHz, MeOD, δ ppm, *J* Hz): δ 4.31 (m, 1H, H-4), 4.10 (t, 1H, $J_{3,2}=J_{3,4}=4.3$, H-3), 3.96 (m, 1H, H-2″), 3.43 (m, 1H, H-2), 3.25 (dd, 1H, $J_{5a,4}=7.0$, $^2J_{5a,5b}=11.6$, H-5a), 3.04 (dd, 1H, $J_{5b,4}=5.9$, H-5b), 3.01–2.94 (m, 2H, H-2′a, H-2′b), 2.86 (m, 1H, H-1″a), 2.72 (m, 1H, H-1″b), 2.08–1.97 (m, 2H, H-1′a, H-1′b), 1.23 (d, 3H, $J_{H,H}=6.3$, H-3″).

(2*S*,3*R*,4*S*)-2-2-2-[(4-Hydroxybutyl)amino]ethylpyrrolidine-3,4-diol (12e). Reductive amination of **25** with *rac*-2-hydroxybutylamine gave, after column chromatography on silica gel (CH_2Cl_2–MeOH 40:1→5:1), protected derivative **27e** (40% yield). Conventional deprotection gave **12e** (83% yield). $[\alpha]_{589}^{25}$ +18 (*c* 0.45, MeOH); IR ν_{max} 3300, 1405, 1095 cm^{-1}; ^1H NMR (400 MHz, MeOD, δ ppm, *J* Hz): δ 4.26 (m, 1H, H-4), 3.97 (t, 1H, $J_{3,2}=J_{3,4}=4.2$, H-3), 3.87 (m, 1H, H-2″), 3.05 (m, 1H, H-2), 3.05 (dd, 1H, $J_{5a,4}=7.2$, $^2J_{5a,5b}=11.5$, H-5a), 2.88 (dd, 1H, $J_{5b,4}=6.1$, H-5b), 2.78 (m, 2H, H-2′a, H-2′b), 2.72 (m, 1H, H-1″a), 2.58 (m, 1H, H-1″b), 1.92 (m, 1H, H-1′a), 1.79 (m, 1H, H-1′b), 1.55–1.41 (m, 2H, H-3″), 1.00 (t, 3H, $J_{H,H}=7.4$, H-4″); ^{13}C NMR (100.5 MHz, MeOD, δ ppm): δ 73.9, 73.4 (C-4, C-3), 72.2 (C-2″), 61.2 (C-2), 55.9 (C-1″), 51.5 (C-5), 47.9 (C-2′), 29.9 (C-1′), 29.3 (C-3″), 10.3 (C-4″). CIMS *m*/*z* 219 [100%, $(M+H)^+\cdot$]. CIMSHR: *m*/*z* 219.1704 (calcd for $C_{10}H_{22}N_2O_3+H$: 219.1709).

(2*S*,3*R*,4*S*)-2-[(Morpholin-4-yl)-ethyl]pyrrolidine-3,4-diol (12f). Reductive amination of **25** with morpholine gave, after column chromatography on silica gel (CH_2Cl_2–MeOH 50:1→30:1), protected derivative **27f** (70% yield). Conventional deprotection gave **12f** (100%

yield). $[\alpha]_{589}^{25}$ +13.6 (*c* 0.67, MeOH); IR ν_{max} 3360, 1690, 1400, 1115 cm^{-1}; ^1H NMR (400 MHz, MeOD, δ ppm, *J* Hz): δ 4.31 (m, 1H, H-4), 4.02 (t, 1H, $J_{3,2}=J_{3,4}=4.0$, H-3), 3.74 (t, 4H, $^3J_{H,H}=4.6$, H-3″), 3.22 (m, 1H, H-2), 3.18 (dd, 1H, $J_{5a,4}=7.4$, $^2J_{5a,5b}=11.5$, H-5a), 2.96 (dd, 1H, $J_{5b,4}=6.6$, H-5b), 2.53 (m, 4H, H-2″), 2.51 (t, 2H, H-2′a, H-2′b), 1.99 (m, 1H, H-1′a), 1.84 (m, 1H, H-1′b); ^{13}C NMR (100.5 MHz, MeOD, δ ppm): δ 73.3, 72.8 (C-4, C-3), 67.7 (C-3″), 61.8 (C-2), 56.9 (C-2′), 54.7 (C-2″), 50.6 (C-5), 26.2 (C-1′). CIMS *m/z* 217 [100%, $(M+H)^+\cdot$]. CIMSHR: *m/z* 217.1550 (calcd for $C_{10}H_{20}N_2O_3+H$: 217.1552).

(2*S*,3*R*,4*S*) - 2 - [2 - (Biphenylamino)ethyl]pyrrolidine-3,4-diol (12g). Reductive amination of **25** with 4-biphenylamine gave, after column chromatography on silica gel (ether–petroleum ether 1:4), protected derivative **27g** (92% yield). Conventional deprotection gave **12g** (52% yield). $[\alpha]_{589}^{25}$ +14 (*c* 0.54, MeOH); IR ν_{max} 3300, 1680, 1610, 1525, 1090, 870, 760, 700 cm^{-1}; ^1H NMR (400 MHz, MeOD, δ ppm, *J* Hz): δ 7.50 (dd, 2H, $^3J_{c,d}=8.5$, H-arom.c), 7.40 (d, 2H, $^3J_{b,a}=8.6$, H-arom.b), 7.33 (t, 2H, H-arom.d), 7.19 (tt, 1H, H-arom. e), 6.72 (d, 2H, H-arom.a), 4.29 (ddd, 1H, $J_{4,3}=4.5$, $J_{4,5a}=7.5$, $J_{4,5b}=7.0$, H-4), 4.00 (dd, 1H, $J_{3,2}=3.8$, H-3), 3.24 (m, 1H, H-2), 3.24 (t, 2H, H-2′a, H-2′b), 3.13 (dd, 1H, $^2J_{5a,5b}=11.5$, H-5a), 2.90 (dd, 1H, H-5b), 2.07 (m, 1H, H-1′a), 1.92 (m, 1H, H-1′b); ^{13}C NMR (100.5 MHz, MeOD, δ ppm): δ 150.1, 143.2, 131.5, 130.2, 129.1, 127.4 and 114.8 (2Ph), 74.0 (C-3), 73.5 (C-4), 61.7 (C-2), 51.3 (C-5), 42.7 (C-2′), 29.8 (C-1′). CIMS: *m/z* 299 [70%, $(M+H)^+\cdot$]. CIMSHR *m/z* 299.1752 (calcd for $C_{18}H_{22}N_2O_2+H$: 299.1760).

***N*-(*tert*-Butoxycarbonyl)-(2*R*,3*R*,4*S*)-2-[2-(Phenylamino)-ethyl]-3,4-*O*-isopropylidene-pyrrolidine-3,4-diol (28a).** To a solution of **24**[26] (80.4 mg, 0.351 mmol) in dry pyridine, $(Boc)_2O$ (84.3 mg, 0.386 mmol) was added. The mixture was left at 20 °C for 2 h. After evaporation of the solvent, the residue was dissolved in AcOEt and washed twice with brine. The dried organic phase was evaporated to afford crude protected compound which was dissolved in dry CH_2Cl_2 (1.75 mL) and cooled to −78 °C. 1M DIBALH in CH_2Cl_2 (475 μL, 0.475 mmol) was added dropwise under an argon atmosphere. After stirring for 3 h, MeOH (0.4 mL) was added and the mixture slowly warmed up to 20 °C. Then, aqueous 1 M HCl (6 mL) was added in an ice-cold bath and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with saturated aqueous solution of $NaHCO_3$ and dried (Na_2SO_4). Evaporation of the solvent afforded crude protected aldehyde **26** which was dissolved in dry 1,2-dichloroethane (1.5 mL) and treated with aniline (40 μL, 0.441 mmol) and $NaBH(OAc)_3$ (86 mg, 0.385 mmol). The reaction mixture was left at 20 °C under Ar atmosphere for 2 h. Then, it was quenched with saturated aqueous solution of $NaHCO_3$. The aqueous phase was extracted with AcOEt and the combined organic phases were dried ($MgSO_4$) and the solvent evaporated in vacuo. The residue was purified by chromatography on silica gel (ether–petroleum ether 1:3→1:2) to afford **28a** (56 mg, 45%).

(2*R*,3*R*,4*S*)-2-[2-(Phenylamino)ethyl]pyrrolidine-3,4-diol (13a). Conventional acidic deprotection of **28a** (38 mg, 0.105 mmol), afforded **13a** (20.4 mg, 88%) as an oil. $[\alpha]_{589}^{25}$ +37 (*c* 1.2, MeOH); IR ν_{max} 3335, 1605, 1505, 1095, 750, 695 cm^{-1}; ^1H NMR (300 MHz, MeOD, δ ppm, *J* Hz): δ 7.12–7.06 (m, 2H, Ph), 6.66–6.58 (m, 3H, Ph), 4.05 (m, 1H, H-4), 3.60 (dd, 1H, $J_{3,2}=5.3$, $J_{3,4}=7.8$, H-3), 3.26–3.18 (m, 3H, H-5a, H-2′a, H-2′b), 3.01 (td, 1H, $J_{2,1'a}=J_{2,1'b}=7.9$, H-2), 2.80 (dd, 1H, $J_{5b,4}=3.4$, $^2J_{5a,5b}=12.2$, H-5b), 1.96 (m, 1H, H-1′a), 1.69 (m, 1H, H-1′b); ^{13}C NMR (75.4 MHz, MeOD, δ ppm): δ 150.1 (C-1 of Ph), 130.0, 118.2 and 114.3 (Ph), 78.3 (C-3), 72.2 (C-4), 61.3 (C-2), 52.4 (C-5), 42.7 (C-2′), 33.8 (C-1′). CIMS: *m/z* 223 [100%, $(M+H)^+\cdot$]. CIMSHR: *m/z* 223.1445 (calcd for $C_{12}H_{18}N_2O_2+H$: 223.1446).

(2*R*,3*S*,4*R*)-2-[2-(Phenylamino)ethyl]pyrrolidine-3,4-diol (*ent*-12a). Reductive amination of *ent*-**25**[25] with aniline gave, after column chromatography on silica gel (ether–petroleum ether 1:4), protected derivative *ent*-**27a** (91% yield). Conventional deprotection gave *ent*-**12a** (100% yield). $[\alpha]_{589}^{25}$ −24 (*c* 0.8, MeOH); CIMS: *m/z* 223 [100%, $(M+H)^+\cdot$]. CIMSHR: *m/z* 223.1442 (calcd for $C_{12}H_{18}N_2O_2+H$: 223.1446). This product showed NMR and IR spectra identical to those of its enantiomer **12a**.

(2*R*,3*S*,4*R*)-2-[2-(Benzylamino)ethyl]pyrrolidine-3,4-diol (*ent*-12b). Reductive amination of *ent*-**25** with benzylamine gave, after column chromatography on silica gel (CH_2Cl_2–MeOH 50:1→10:1), protected derivative *ent*-**27b** (54% yield). Conventional deprotection gave *ent*-**12b** (66% yield). $[\alpha]_{589}^{25}$ −26 (*c* 0.73, MeOH). CIMS: *m/z* 237 [100%, $(M+H)^+\cdot$]. CIMSHR: *m/z* 237.1601 (calcd for $C_{13}H_{20}N_2O_2+H$: 237.1603). This product showed NMR and IR spectra identical to those of its enantiomer **12b**.

(2*R*,3*S*,4*R*)-2-[(Morpholin-4-yl)-ethyl]pyrrolidine-3,4-diol (*ent*-12f). Reductive amination of *ent*-**25** with morpholine gave, after column chromatography on silica gel (CH_2Cl_2–MeOH 50:1→20:1), protected derivative *ent*-**27f** (91% yield). Conventional deprotection gave *ent*-**12f** (70% yield). $[\alpha]_{589}^{25}$ −10 (*c* 0.49, MeOH). CIMS: *m/z* 217 [100%, $(M+H)^+\cdot$]. CIMSHR: *m/z* 217.1550 (calcd for $C_{10}H_{20}N_2O_3+H$: 217.1552). This product showed NMR and IR spectra identical to those of its enantiomer **12f**.

(2*R*,3*S*,4*R*) - 2 - [(4 - Hydroxybutylamino)ethyl]pyrrolidine-3,4-diol (*ent*-12h). Reductive amination of *ent*-**25** with 4-hydroxybutylamine gave, after column chromatography on silica gel (CH_2Cl_2–MeOH 30:1), protected derivative *ent*-**27h** (20% yield). Conventional deprotection gave *ent*-**12h** (92% yield). $[\alpha]_{589}^{25}$ −10 (*c* 0.48, MeOH); IR ν_{max} 3285, 1400, 1095 cm^{-1}; ^1H NMR (400 MHz, MeOD, δ ppm, *J* Hz): δ 4.24 (m, 1H, H-4), 3.97 (t, 1H, $J_{3,2}=J_{3,4}=4.3$, H-3), 3.61 (t, 2H, $J_{H,H}=6.0$, H-4″), 3.05 (m, 1H, H-2), 3.05 (dd, 1H, $J_{5a,4}=7.2$, $^2J_{5a,5b}=11.5$, H-5a), 2.87 (dd, 1H, $J_{5b,4}=6.1$, H-5b), 2.80 (t, 2H, H-2′a, H-2′b), 2.72 (t, 2H, $^3J_{H,H}=6.8$, H-1″), 1.93 (m, 1H, H-1′a), 1.79 (m, 1H, H-1′b), 1.70–1.58 (m, 4H, H-2″, H-3″); ^{13}C NMR (100.5 MHz, MeOD, δ

ppm): δ 73.8, 73.3 (C-4, C-3), 62.6 (C-4″), 61.0 (C-2), 51.5 (C-5), 50.1 (C-1″), 47.8 (C-2′), 29.5 (C-1′), 31.4, 26.7 (C-2″, C-3″). CIMS: *m*/*z* 219 [45%, $(M+H)^{+}\cdot$]. CIMSHR: *m*/*z* 219.1706 (calcd for $C_{10}H_{22}N_2O_3+H$: 219.1709).

***N*-(*tert*-Butoxycarbonyl)-(2*S*,3*S*,4*R*)-2-[2-(Phenylamino)-ethyl]-3,4-*O*-isopropylidene-pyrrolidine-3,4-diol (*ent*-28a).** To a solution of *ent*-**24**[26] (70 mg, 0.306 mmol) in dry pyridine (1.5 mL), $(Boc)_2O$ (73.5 mg, 0.337 mmol) was added. The mixture was left at 20 °C for 2 h. After evaporation of the solvent, the residue was dissolved in AcOEt and washed twice with brine. The dried organic phase ($MgSO_4$) was evaporated to afford crude protected compound which was dissolved in dry CH_2Cl_2 (1.5 mL) and cooled to −78 °C. 1 M DIBALH in CH_2Cl_2 (405 μL, 0.405 mmol) was added dropwise under an Ar atmosphere. After stirring for 3 h, MeOH (0.35 mL) was added and the mixture slowly warmed up to 20 °C. Then, aqueous 1 M HCl (3 mL) was added in an ice-cold bath and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated aqueous solution of $NaHCO_3$ and dried (Na_2SO_4). Evaporation of the solvent afforded crude protected aldehyde *ent*-**26**. Reductive amination with aniline gave, after column chromatography on silica gel (ether–petroleum ether 1:3→1:2), *ent*-**28a** (61.2 mg, 55%).

(2*S*,3*S*,4*R*)-2-[2-(Phenylamino)ethyl]pyrrolidine-3,4-diol (*ent*-13a). Conventional acidic deprotection of *ent*-**28a** (51.5 mg, 0.142 mmol), afforded *ent*-**13a** (26.6 mg, 84%) as an oil. $[\alpha]_{589}^{25}$ −43 (*c* 0.9, MeOH). CIMS: *m*/*z* 223 [100%, $(M+H)^{+}\cdot$]. CIMSHR: *m*/*z* 223.1442 (calcd for $C_{12}H_{18}N_2O_2+H$: 223.1446). This product showed NMR and IR spectra identical to those of its enantiomer **13a**.

***N*-(*tert*-Butoxycarbonyl)-(2*S*,3*R*,4*S*)-2-(Benzylamino)methyl-3,4-*O*-isopropylidene-pyrrolidine-3,4-diol (31b).** Reductive amination of aldehyde **30**[7b] (111 mg, 0.41 mmol) with benzylamine gave, after flash chromatography (AcOEt), protected derivative **31b** (114 mg, 77% yield). $[\alpha]_{589}^{25}$ 24 (*c* 0.47, CH_2Cl_2). UV (MeCN): λ_{max} 217 (ε = 5918). IR (film) ν_{max} 2980, 2935, 1695, 1495, 1455, 1395, 1245, 1210, 1165, 1115, 1085, 860, 735, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ ppm, *J* Hz): δ 7.43–7.21 (m, 5H arom), 4.80 (t, 1H, $^3J_{3,4}=6.7$, $^3J_{3,2}=6.7$, H-3), 4.71 (m, 1H, H-4), 4.06 (m, 1H, H-2), 3.83 (m, 2H, CH_2-Ph), 3.80 (m, 1H, H-5a), 3.33 (dd, 1H, $^3J_{5a,4}=3.7$, $^2J_{5a,5b}=12.4$, H-5a), 2.88 (m, 2H, H-1′a, H-1′b), 1.47 (s, 3H, $C(CH_3)_2$), 1.42 (s, 9H, $(CH_3)_3C$), 1.34 (s, 3H, $C(CH_3)_2$); ^{13}C NMR (100.5 MHz, $CDCl_3$, δ ppm): δ 154.4 (C=O of Boc), 140.4, 128.3, 128.1, 126.8 (C arom), 112.7 ($C(CH_3)_2$), 80.2 (C-3), 80.0 ($C(CH_3)_3$), 77.9 (C-4), 59.3 (C-2), 54.0 (CH_2-Ph), 50.6 (C-5), 48.9 (C-1′), 28.4 ($(CH_3)_3C$), 26.3 ($(CH_3)_2C$) 25.0 ($(CH_3)_2C$)). CI-MS (NH_3): 363 ($M+H^+$, 7), 307 (13), 263 (6), 215 (3), 187 (14), 142 (11), 120 (51), 91 (100). Anal. calcd for $C_{20}H_{30}N_2O_4$ (362.49): C 66.27, H 8.34, N 7.73 ; found C 66.50, H 8.28, N 7.63.

(2*S*, 3*R*, 4*S*)-2-[(Benzylamino)methyl] pyrrolidine-3,4-diol (14b). Following the general deprotection procedure starting from **31b** (21 mg, 0.06 mmol) in 2 mL of $CF_3COOH–H_2O$ (4/1). The crude product was purified by flash chromatography (MeCN–ammonium hydroxide 4:1) affording **14b** (13 mg, 100%). $[\alpha]_{577}^{25}$ +6, $[\alpha]_{546}^{25}$ +6, $[\alpha]_{435}^{25}$ +7, $[\alpha]_{405}^{25}$ +9 (*c* = 0.47, MeOH). UV (MeCN): λ_{max} 312 (ε = 2506), 260 (ε = 2268), 212 (ε = 6919). IR (film) ν_{max}: 3060, 1670, 1435, 1200, 1130, 840, 800, 725 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ ppm, *J* Hz): δ 7.57 (m, 5H arom), 4.55 (m, 1H, H- 4), 4.49 (m, 1H, H-3), 4.32 (s, 2H, CH_2-Ph), 3.96 (m, 1H, H-2), 3.55 (m, 2H, H-1′a, H-5a), 3.42 (dd, 1H, $^3J_{1'b,2}=6.3$, $^2J_{1'a,1'b}=13.8$, H-1′b), 3.27 (dd, 1H, $^3J_{5b,4}=6.3$, $^2J_{5b,5a}=11.9$, H-5b).^{13}C NMR (100.5 MHz, $CDCl_3$, δ ppm): δ 129.6 (C arom), 129.4 (C arom), 129.3 (C arom), 70.6 (C-3), 70.3 (C-4), 57.1 (C-2), 52.0 (CH_2-Ph), 48.1 (C-5), 44.7 (C-1′). CI-MS (NH_3): 223 ($M+H^+$, 100), 222 (M^+), 187 (1), 150 (5), 136 (15), 121 (49), 106 (28), 91 (77).

***N*-(*tert*-Butoxycarbonyl)-(2*S*,3*R*,4*S*)-2-(inden-1-ylamino)-methyl-3,4-*O*-isopropylidene-pyrrolidine-3,4-diol (31i).** Reductive amination of aldehyde **30** (94 mg, 0.35 mmol) with (*R*)-1-aminoindane gave, after flash chromatography (AcOEt), protected derivative **31i** (86 mg, 64% yield). $[\alpha]_{589}^{25}$ +29, $[\alpha]_{577}^{25}$ +34, $[\alpha]_{546}^{25}$ +40, $[\alpha]_{435}^{25}$ +64, $[\alpha]_{405}^{25}$ +77 (*c* = 0.40, CH_2Cl_2).UV (MeCN): λ_{max} 272 (ε = 3155), 266 (ε = 3220), 206 (ε = 19627). IR (film) ν_{max}: 3340, 2980, 2935, 1695, 1475, 1460, 1395, 1250, 1210, 1165, 1120, 1085, 1000, 860, 750. ^1H NMR (400 MHz, MeOD, δ ppm, *J* Hz): δ 7.34 (m, 1H arom), 7.27–7.16 (m, 3H arom), 4.80 (dd, 1H, $^3J_{3,4}=6.7$, $^3J_{3,2}=6.7$, H-3), 4.72 (m, 1H, H-4), 4.26 (dd, 1H, $^3J_{1''a,2''a}=6.5$, $^3J_{1''a,1''b}=6.5$, H- 1″a), 4.06 (m, 1H, H-2), 3.79 (m, 1H, H-5a), 3.36 (dd, 1H, $^3J_{5b,4}=3.6$, $^2J_{5b,5a}=12.5$, H-5b), 2.99 (m, 3H, H-3″a, H-1′a, H-1′b), 2.82 (m, 1H, H-3″b), 2.34 (m, 1H, H-2″a), 1.89 (m, 1H, H-2″b), 1.45 (s, 3H, CH_3), 1.44 (s, 9H, $(CH_3)_3C$), 1.33 (s, 3H, CH_3). ^{13}C NMR (101 MHz, MeOD, δ ppm): δ 154.4 (C=O of Boc), 145.0 (C arom), 143.5 (C arom), 127.3 (C arom), 126.2 (C arom), 124.7 (C arom), 124.1 (C arom), 112.7 ($C(CH_3)_2$), 80.3 (C-3), 80.0 ($C(CH_3)_3$), 77.9 (C-4), 63.4 (C-1″), 59.9 (C-4), 50.7 (C-6), 47.1 (C-1′), 33.2 (C-2″), 30.4 (C-3″), 28.4 ($(CH_3)_3C$), 26.2 ($(CH_3)_2C$), 25.0 ($(CH_3)_2C$). CI-MS (NH_3): 389 ($M+H^+$, 100), 388 (M^+, 81), 333 (9), 215 (2), 132 (10), 117 (18), 84 (2). Anal. calcd for $C_{22}H_{32}N_2O_4$ (388.53): C 68.01, H 8.30, N 7.21 ; found C 68.14, H 8.23.

(2*S*,3*R*,4*S*)-2-[(inden-1-ylamino)methyl]pyrrolidine-3,4-diol (14b). Following the general deprotection procedure starting from **31i** (22 mg, 0.06 mmol) in 2.5 mL of $CF_3COOH–H_2O$ (4/1). The crude product was purified by flash chromatography (MeCN–ammonium hydroxide 4:1) affording **14i** (14 mg, 100%). $[\alpha]_{589}^{25}$ +0.6, $[\alpha]_{577}^{25}$ +0.9 (*c* = 0.47, MeOH). UV (MeCN): λ_{max} 331 (ε = 389), 200 (ε = 4355). IR (KBr) ν_{max}: 3105, 1670, 1475, 1435, 1400, 1205, 1130, 840, 800, 755, 725 cm^{-1}. ^1H NMR (400 MHz, MeOD, δ ppm, *J* Hz): δ 7.60 (d, 1H, $^3J=7.5$, H arom), 7.48–7.29 (m, 3H arom), 4.75 (dd, 1H, $^3J_{1''a,2''a}=4.3$, $^3J_{1''a,2''b}=7.1$, H-1″a), 4.38 (m, 2H, H-3, H-4), 3.94 (ddd, 1H, $^3J_{2,1'a}=5.3$, $^3J_{2,3}=5.4$, $^3J_{2,1'}=6.3$, H-2), 3.59 (dd, 1H,

$^{3}J_{1'a,2}=5.3$, $^{2}J_{1'a,1'b}=13.3$, H-1′a), 3.45 (dd, 1H, $^{3}J_{1'b,2}=6.3$, H-1′b), 3.42 (m, 1H, H-5a), 3.26–3.18 (m, 2H, H-5b, H-3″a), 3.00 (ddd, 1H, $^{3}J_{3''b,2''a}=4.7$, $^{3}J_{3''b,2''b}=8.7$, $^{2}J_{gem}=13.5$, H-3″b), 2.58 (m, 1H, H-2″a), 2.30 (m, 1H, H-2″b). ^{13}C NMR (101 MHz, MeOD, δ ppm): δ 147.0 (C arom), 139.9 (C arom), 131.7 (C arom), 128.9 (C arom), 127.3 (C arom), 73.1 (C-3), 72.6 (C-4), 65.7 (C-1″), 59.7 (C-2), 50-49 (C-5), 45.1 (C-1′), 32.0 (C-3″), 31.2 (C-2″). CI-MS (NH_3): 249 ($M+H^+$, 100), 211 (2), 162 (3), 146 (23), 132 (23), 117 (78), 91 (12).

(2*S*,3*R*,4*S*)-2-[2-(Biphenylmethylamino)ethyl]pyrrolidine-3,4-diol dihydrochloride (12j). Reductive amination of diamine **32**[25] (88 mg, 0.308 mmol) and 4-biphenylcarboxaldehyde (51 mg, 0.28 mmol) gave, after column chromatography on silica gel (CH_2Cl_2–MeOH 40:1→30:1), protected derivative **33** (85 mg, 61%). Acidic deprotection with aqueous 4 M HCl gave **12j** (34 mg, 100% yield). ^{13}C NMR (75.4 MHz, DMSO-d_6, δ ppm): δ 140.6, 139.4, 131.0, 130.8, 129.0, 127.8, 126.8, 126.7 (2Ph), 70.3, 69.7 (C-3, C-4), 58.0 (CH_2-Ph), 49.6 (C-2), 46.2 (C-5), 43.4 (C-2′), 23.2 (C-1′). CIMSHR: *m*/*z* 313.1907 (calcd for $C_{19}H_{24}N_2O_2+H$: 313.1916).

***N*-(α-Naphtyl)-*N*-(*tert*-butoxycarbonyl)-2,3,6-trideoxy-3,6-imine-4,5-*O*-isopropylidene-L-*arabino*-hexanamide (35k).** A solution of **23**[26b] (370 mg, 1.125 mmol) in ethanolic 1 M NaOH (30 mL) was heated at 40 °C for 5 h. Then, the mixture was neutralized with IRA-120 (H^+) resin, filtered and the filtrate concentrated. Purification of the residue by chromatography on silica gel (ether–petroleum ether 2:1) gave **34** (250 mg, 74%) as an oil. To a solution of **34** (128 mg, 0.425 mmol) in DMF (3.5 mL) were added PyBOP (298 mg, 0.552 mmol), $(iPr)_2NEt$ (96 μL, 0.552 mmol) and α-naphthylamine (92 mg, 0.552 mmol). After stirring at 20 °C for 24 h, the mixture was concentrated and the residue diluted with CH_2Cl_2 and then washed with aqueous 1 M HCl, then with a saturated aqueous solution of $NaHCO_3$ and finally with brine. The dried organic phase ($MgSO_4$) was purified by chromatography on silica gel (ether–petroleum ether 1:1) to give **35k** (116 mg, 64%) as a solid. $[\alpha]_{589}^{25}$ +59 (*c* 1, CH_2Cl_2); IR ν_{max} 3290, 1695, 1670, 1535, 1400, 1165, 1120, 990, 865, 775 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6 90 °C, δ ppm, *J* Hz): δ 9.50 (bs, 1H, NH), 8.13 (m, 1H, H-arom.), 7.90 (m, 1H, H-arom.), 7.72 (d, 1H, *J* = 8.1, H-arom.), 7.68 (d, 1H, *J* = 8.1, H-arom.), 7.53–7.43 (m, 3H, H-arom.), 4.81 (t, 1H, $J_{3,4}=J_{3,2}=6.1$, H-3), 4.75 (td, 1H, $J_{4,5a}=6.3$, $J_{4,5b}=3.0$, H-4), 4.27 (ddd, 1H, $J_{2,1'a}=4.8$, $J_{2,1'b}=9.3$, H-2), 3.65 (dd, 1H, $^{2}J_{5a,5b}=12.3$, H-5a), 3.31 (dd, 1H, H-5b), 3.13 (dd, 1H, $^{2}J_{1'a,1'b}=15.3$, H-1′a), 2.84 (dd, 1H, H-1′b), 1.51 and 1.31 (2s, $C(CH_3)_2$), 1.42 (s, $C(CH_3)_3$). ^{13}C NMR (75.4 MHz, DMSO-d_6 90 °C, δ ppm): δ 169.4 (NHCO), 153.5 (C=O of Boc), 133.6 (Cq of Ph), 133.4 (Cq of Ph), 127.8 (Cq of Ph), 127.4, 125.3, 124.9, 124.5, 122.5, 121.1 (Ph), 111.0 ($C(CH_3)_2$), 79.4 (C-3), 78.6 ($C(CH_3)_3$), 76.7 (C-4), 56.4 (C-2), 50.5 (C-5), 35.5 (C-1′), 27.7 ($C(CH_3)_3$), 25.9 and 24.6 ($C(CH_3)_2$). FABMS: *m*/*z* 426 [100%, $(M+Na)^+$]. CIMSHR *m*/*z* 426.2138 (calcd for $C_{24}H_{30}N_2O_5$: 426.2155).

(2*S*,3*R*,4*S*)-2-[2-(Naphtylamino)ethyl]pyrrolidine-3,4-diol dihydrochloride (12k). To a 0 °C solution of amide **35k** (50 mg, 0.117 mmol) in dry THF (3 mL), $BH_3.SMe_2$ (1 M in THF) (0.585 mL) was added dropwise under Ar atmosphere and the reaction mixture was heated under reflux for 2 h. After cooling, the excess of reducing agent was quenched by slow addition of MeOH (3 mL). After evaporation of the solvent, the residue was purified by column cromatography (ether–petroleum ether 1:5) to give the corresponding protected diamine (35 mg, 73%). Acidic deprotection of the substrate (15 mg, 0.036 mmol) with 1 M HCl in 1:1 H_2O/THF (1 mL) gave **12k** (12 mg, 100%). ^{1}H NMR (300 MHz, MeOD, δ ppm, *J* Hz): δ 8.13 (dd, 1H, *J* = 0.9, *J* = 7.8, H-arom.), 8.04 (dd, 2H, *J* = 0.6, *J* = 8.1, H-arom.), 7.98 (bd, 1H, H-arom.), 7.76–7.56 (m, 4H, H-arom.), 4.39 (td, 1H, $J_{4,3}=3.8$, $J_{4,5a}=J_{4,5b}=7.5$, H-4), 4.16 (t, 1H, $J_{3,2}=3.8$, H-3), 3.73–3.68 (m, 3H, H-2, H-2′a, H-2′b), 3.43 (dd, 1H, $^{2}J_{5a,5b}=11.7$, H-5a), 3.10 (dd, 1H, H-5b), 2.50 (m, 1H, H-1′a), 2.32 (m, 1H, H-1′b); ^{13}C NMR (75.4 MHz, MeOD, δ ppm): δ 136.1, 133.8, 130.3, 128.9, 128.4, 126.7, 126.4 and 121.4 (Ar), 71.8, 71.4 (C-3, C-4), 60.5 (C-2), 49.1 (C-5), 48.0 (C-2′), 25.4 (C-1′). FABMS: *m*/*z* 273 [100%, $(M+H)^+$], 295 [40%, $(M+H)^+$].

***N*-(1′-Biphenyl)-*N*-(*tert*-butoxycarbonyl)-2,3,6-trideoxy-3,6-imine-4,5-*O*-isopropylidene-D-*arabino*-hexanamide (*ent*-35g).** A solution of *ent*-**23** (565 mg, 1.717 mmol) in 1 M NaOH in 2:1 EtOH–H_2O (45 mL) was heated at 40 °C for 5 h. Then, the mixture was neutralized with IRA-120 (H^+) resin, filtered and the filtrate concentrated. To a solution of the crude acid *ent*-**34** (200 mg) in DMF (6.5 mL) were added PyBOP (463 mg, 0.863 mmol), $(iPr)_2NEt$ (150 μL, 0.863 mmol) and biphenylamine (149 mg, 0.863 mmol). After stirring at 20 °C for 24 h, the mixture was concentrated and the residue diluted with CH_2Cl_2 and sequentially washed with aqueous 1 M HCl, aqueous saturated solution of $NaHCO_3$ and brine. The dried organic phase ($MgSO_4$) was purified by chromatography on silica gel (ether–petroleum ether 1:1) to give *ent*-**35g** (234 mg, 78%) as a solid. $[\alpha]_{589}^{25}$ −52.8 (c 0.7, CH_2Cl_2); IR ν_{max} 3320, 1695, 1670, 1530, 1400, 1165, 1120, 990, 860, 765; ^{1}H NMR (300 MHz, DMSO-d_6 90 °C, δ ppm, *J* Hz): δ 9.62 (bs, 1H, NH), 7.67–7.54 (m, 5H, H-arom.), 7.45–7.40 (m, 3H, H-arom.), 7.30 (m, 1H, H-arom.), 4.80 (t, 1H, $J_{3,4}=J_{3,2}=6.3$, H-3), 4.74 (td, 1H, $J_{4,5a}=6.6$, $J_{4,5b}=3.0$, H-4), 4.25 (ddd, 1H, $J_{2,1'a}=4.6$, $J_{2,1'b}=8.8$, H-2), 3.64 (dd, 1H, $^{2}J_{5a,5b}=12.6$, H-5a), 3.30 (dd, 1H, H-5b), 2.97 (dd, 1H, $^{2}J_{1'a,1'b}=15.6$, H-1′a), 2.70 (dd, 1H, H-1′b), 1.46 and 1.28 (2s, $C(CH_3)_2$), 1.39 (s, $C(CH_3)_3$). ^{13}C NMR (75.4 MHz, DMSO-d_6 90 °C, δ ppm): δ 168.7 (NHCO), 153.4 (C=O of Boc), 139.5 (Cq of Ph), 138.4 (Cq of Ph), 134.3 (Cq of Ph), 128.2, 126.3, 126.2, 125.7, 119.2 (Ph), 111.1 ($C(CH_3)_2$), 79.3 (C-3), 78.6 ($C(CH_3)_3$), 76.8 (C-4), 56.2 (C-2), 50.3 (C-5), 35.9 (C-1′), 27.6 ($C(CH_3)_3$), 25.8 and 24.5 ($C(CH_3)_2$). FABMS: *m*/*z* 452 [55%, $(M+Na)^+$].

(2*R*,3*S*,4*R*)-2-[2-(Biphenylamino)ethyl]pyrrolidine-3,4-diol dihydrochloride (*ent*-12g). To a solution of amide *ent*-**35g** (50 mg, 0.111 mmol) in dry THF (3 mL) stirred at 0 °C, $BH_3.SMe_2$ (1 M in THF) (0.553 mL) was added dropwise under Ar atmosphere and the reaction mixture

was heated under reflux for 1 h. After cooling, the excess of reducing agent was quenched by slow addition of MeOH (3 mL). After evaporation of the solvent, the residue was purified by column cromatography (ether–petroleum ether 1:4) to afford the corresponding protected diamine (41.8 mg, 86%). Acidic deprotection of the substrate (16 mg, 0.036 mmol) with 1 M HCl in 1:1 H_2O / THF (1 mL) gave *ent*-**12g** (12.8 mg, 94%). ^1H NMR (500 MHz, MeOD, δ ppm, *J* Hz): δ 7.82 (bd, 2H, $J=8.5$, H-arom.), 7.62 (m, 4H, H-arom.), 7.47 (bt, 2H, $J=8.5$, H-arom.), 7.39 (tt, 1H, $J=1.5$, $J=8.5$, H-arom.), 4.42 (td, 1H, $J_{4,3}=3.8$, $J_{4,5a}=J_{4,5b}=7.4$, H-4), 4.19 (t, 1H, $J_{3,2}=3.8$, H-3), 3.72 (m, 1H, H-2), 3.61–3.55 (m, 2H, H-2′a, H-2′b), 3.45 (dd, 1H, $^2J_{5a,5b}=11.7$, H-5a), 3.12 (dd, 1H, H-5b), 2.42 (m, 1H, H-1′a), 2.24 (m, 1H, H-1′b); ^{13}C NMR (125.5 MHz, MeOD, δ ppm): δ 143.8, 140.6, 136.1, 130.2, 130.0, 129.3, 128.1 and 123.9 (2Ph), 71.9 (C-4), 71.3 (C-3), 60.4 (C-2), 49.1 (C-5, C-2′), 25.0 (C-1′). CIMS: *m*/*z* 298 [30%, $(M+H)^+$·]. CIMSHR: *m*/*z* 298.1670 (calcd for $C_{18}H_{22}N_2O_2$: 298.1681).

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References and Notes

1. (a) Elbein, A. D.; Molyneux, R. J. In *Iminosugars as Glycosidase Inhibitors; Nojirimycin and Beyond*, Ed. A.E. Stütz, Wiley-VCH, Weinheim, **1999**, pp 216–251. (b) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron:Assymetry* **2000**, *11*, 1645. (c) Asano, N. J. *Enzyme Inhib*. **2000**, *15*, 215.
2. For inhibitory activities of 1,4-iminopentitols and 1,4-iminohexitols, see for example El Ashry, E. S. H.; Raashed, N.; Shobier, H. S. *Pharmazie* **2000**, *55*, 331.
3. Vasella, A. T.; Heigtman, T. D. *Angew. Chem., Int. Ed. Engl*. **1999**, *38*, 750.
4. (a) Lipper, R. A. *Modern Drug Discovery* **1999**, 55. (b) Lipinsky, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Delivery Rev*. **1997**, *23*, 3.
5. (a) Johnson, C. R.; Miller, M. W.; Golebiowski, A.; Sundram, H.; Ksebati, M. B. *Tetrahedron Lett*. **1994**, *35*, 8991. (b) Johns, B. A.; Pan, Y. T.; Elbein, A. D.; Johnson, C. R. *J. Am. Chem. Soc*. **1997**, *119*, 4856. (c) Leewenburgh, M. A.; Picasso, S.; Overkleeft, H. S.; van der Marel, G. A.; Vogel, P.; van Boom, J. H. *Eur. J. Org. Chem*. **1999**, 1185. (d) Martin, O. R.; Liu, L.; Yang, F. *Tetrahedron Lett*. **1996**, *37*, 1991. (e) Saavedra, O. M.; Martin, O. *J. Org. Chem*. **1996**, *61*, 6987. (f) Baudat, A.; Vogel, P. *Tetrahedron Lett*. **1996**, *37*, 483. (g) Baudat, A.; Vogel, P. *J. Org. Chem*. **1997**, *62*, 6252. (h) Frerot, E.; Marquis, C.; Vogel, P. *J. Org. Chem*. **1997**, *62*, 6252. (i) Kraehenbuehl, K.; Picasso, S.; Vogel, P. *Helv. Chim. Acta* **1998**, *81*, 1439. (j) Zhu, Y.-H.; Vogel, P. *J. Org. Chem*. **1999**, *64*, 666. (k) Marquis, C.; Picasso, S.; Vogel, P. *Synthesis* **1999**, 1441. (l) Zhu, Y.-H.; Vogel, P. *J. Chem. Soc. Chem. Commun*. **1999**, 1873. (m) Cardona, F.; Robina, I.; Vogel, P. *J. Carbohydr. Chem*. **2000**, *19*, 555. (n) Marquis, C.; Cardona, F.; Robina, I.; Wurth, G.; Vogel, P. *Heterocycles* **2002**, *56*, 181. (o) Cardona, F.; Valenza, S.; Picasso, S.; Goti, A.; Brandi, A. *J. Org. Chem*. **1998**, *63*, 7311. (p) Navarro, I.; Vogel, P. *Helv. Chem. Acta* **2002**, *85*, 152.
6. (a) Robina, I.; Moreno-Vargas, A. J.; Fernández-Bolaños, J. G.; Fuentes, J.; Demange, R.; Vogel, P. *Bioorg. Med. Chem. Lett*. **2001**, *11*, 2555. (b) Moreno-Vargas, A. J.; Demange, R.; Fuentes, J.; Robina, I.; Vogel, P. *Bioorg. Med. Chem. Lett*. **2002**, *12*, 2335. (c) Moreno-Vargas, A. J.; Robina, I.; Demange, R. ; Vogel, P. *Helv. Chim. Acta*, in press.
7. (a) Popowycz, F.; Gerber-Lemaire, S.; Demange, R.; Rodríguez-García, E.; Carmona Asenjo, A. T.; Robina, I.; Vogel, P. *Bioorg. Med. Chem. Lett*. **2001**, *11*, 2489. (b) Popowycz, F.; Gerber-Lemaire, S.; Rodríguez-García, E.; Schütz, C.; Vogel, P. *Helv. Chim Acta*. in press.
8. Behr, J.-B.; Chevrier, C.; Defoin, A.; Tarnus, C.; Streith, J. *Tetrahedron* **2003**, *59*, 543.
9. Gerber-Lemaire, S.; Popowycz, F.; Rodríguez-García, E.; Carmona Asenjo, A. T.; Robina, I.; Vogel, P. *ChemBioChem*. **2002**, *3*, 466.
10. Kieβ, F.-M.; Poggendorf, O.; Picasso, S.; Jäger, V. *J. Chem. Soc. Chem. Commun*. **1998**, 119.
11. Reynolds, R. C.; Bansal, N.; Rose, J.; Friedrich, J.; Suling, W. J.; Maddry, J. A. *Carbohydr. Res*. **1999**, *317*, 164.
12. Wrodnigg, T. M.; Gaderbauer, W.; Greimel, P.; Häusler, H.; Sprenger, F. K.; Stütz, A. E.; Virgona, C.; Withers, S. G. *J. Carbohydr. Chem*. **2000**, *19*, 975.
13. Wrodnigg, T. M.; Withers, S. G.; Stütz, A. E. *Biorg. Med. Chem. Lett*. **2001**, *11*, 1063.
14. Takebayashi, M.; Hiranuma, S.; Kanie, Y.; Kajimoto, T.; Kanie, O.; Wong, C.-H. *J. Org. Chem*. **1999**, *64*, 5280.
15. Saotome, C.; Wong, C.-H.; Kanie, O. *Chemistry&Biology* **2001**, *8*, 1061.
16. Joubert, M.; Defoin, A.; Tarnus, C.; Streith, J. *Synlett* **2000**, 1366.
17. Moreno-Vargas, A. J.; Vogel, P. *Tetrahedron Lett*. **2003**, *44*, 5069.
18. El Nemr, A. *Tetrahedron* **2000**, *56*, 8579 and reference therein.
19. Ganem, B.; King, S. B. *J. Am. Chem. Soc*. **1994**, *116*, 562.
20. (a) For swainsonine, see for example: Goss, P. E.; Reid, C. L.; Bailey, D.; Dennis, J. W. *Clin. Cancer. Res*. **1997**, *3*, 1077. (b) Rye, P. D.; Bovin, N. V.; Vlasova, E. V.; Walker, R. A. *Glycobiology* **1995**, *5*, 385. (a) For mannostatin, see for example: Fellows, L. E. *New. Sci*. **1989**, *123*, 45. (b) Trugan, G.; Rousset, M.; Zweibaum, A. *FEBS Lett*. **1986**, *195*, 28. (c) Humphries, M. J.; Matsumoto, K.; White, S. L.; Molyneux, R. J.; Olden, K. *Cancer Res*. **1988**, *48*, 1410.
21. (a) Dedera, D.; van der Heyden, N.; Ratner, L. *AIDS Res. Hum. Retroviruses* **1990**, *6*, 789. (b) Fischer, P. B.; Collin, M.; Karlsson, G. B.; James, W.; Butters, T. D.; Davis, S. J.; Gordon, S.; Dwek, R. A.; Platt, F. M. *J. Virol*. **1995**, *69*, 5791.
22. (a) Sunkara, P. S.; Bowlin, T. L.; Liu, P. S.; Sjoerdsma, A. *Biochem. Biophys. Res. Commun*. **1987**, *148*, 206. (b) Karpas, A.; Fleet, G. W.; Dwek, R. A.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Jacob, G. S.; Rademacher, T. W. *Proc. Natl. Acad. Sci. U.S.A*. **1988**, *85*, 9229. (c) Ratner, L.; Van der Heyden, N.; Dedera, D. *Virology* **1991**, *181*, 180. (d) Walker, B. D.; Kowalski, M.; Goh, W. C.; Kozarsky, K.; Krieger, M.; Rosen, C.; Rohrschneider, L.; Haseltine, W. A.; Sodroski, J. *Proc. Natl. Acad. Sci. U.S.A*. **1987**, *84*, 8120.
23. Ogawa, S. Patent Appl.: JP 2001-7317520010314, *Chem. Abstr*. **2002**, *137*, 247880.
24. Jacob, G. S. *Curr. Opin. Struct. Biol*. **1995**, *5*, 605.
25. Gerber-Lemaire, S.; Popowycz, F.; Rodríguez-García, E.;

Schütz, C.; Carmona-Asenjo, A. T.; Robina, I.; Vogel, P. *Arkivok* **2002**, *xii*, 23.
26. (a) Robina, I.; Gearing, R. P.; Buchanan, J. G.; Whightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2622. (b) Thompson, D. K.; Hubert, C. N.; Whightman, R. H. *Tetrahedron* **1993**, *49*, 3827.
27. (a) Kim, D.-K.; Kim, Y-W.; Kim, H-T.; Kim, K. H. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 643. (b) Kim, D.-K.; Kim, G.; Kim, Y-W. *J. Chem. Soc., Perkin Trans. 1* **1996**, 803.
28. Hadjuk, P. J.; Bures, M.; Praestgaard, V.; Fesik, S. W. *J. Med. Chem*. **2000**, *43*, 3443.
29. (a) Picasso, S.; Chen, Y.; Vogel, P. *Carbohydr. Lett*. **1994**, *1*, 1. (b) Chen, Y.; Vogel, P. *J. Org. Chem*. **1994**, *59*, 2487. (c) Brandi, A.; Cicchi, S.; Cordero, F. M.; Frigneoli, B.; Goti, A.; Picasso, S.; Vogel, P. *J. Org. Chem*. **1995**, *60*, 6806.
30. Martin, O. R.; Saavedra, O. M.; Xie, F.; Liu, L.; Picasso, S.; Vogel, P.; Kizu, H.; Asano, N. *Bioorg. Med. Chem*. **2001**, *9*, 1269.